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FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/754,446	SUN ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *1-18,35 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-34* is/are rejected.

7)☒ Claim(s) *21 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-36 are pending.

Applicant's election without traverse of Group III, claims 19-34, filed on 19 Dec. 2005 is acknowledged.

Claims 1-18 and 35-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 19-34 are examined on the merits.

The claim numbers referred to in this office action are in correspondence with the claims as renumbered, pursuant to 37 CFR 1.126, as described in the Requirement for Restriction of 21 Nov. 2005.

Information Disclosure Statement

1. The IDS filled on 28 June 2004 has been considered. Citation A1 (US Patent 6,028,290) has been considered but it is noted that this patent document does not appear to be relevant to the instant application. The cited reference appears in the specification (p.10) with regard to methods and compositions for detectably labeling molecules, however the '290 patent describes an arc welding apparatus.

Specification

2. The instant application attempts to incorporate the sequence of the human MCOLN1 gene by reference to GenBank accession number AF287270, particularly with regard to the locations of mutations (p.1, paragraph[0004], p.6, paragraph[0022]); , and the locations of hybridization of primers (p.9, paragraphs[0035]-[0036]; Table 1) and probes (p.13, paragraph[0050]; Table 2). The attempt to incorporate subject matter into this application by reference to GenBank AF287270 (the MCOLN1 gene sequence) is

ineffective because the information contained in the reference is essential for the claimed invention; for example the sequence information is essential for claims that recite specific nucleotide positions for primer and probe hybridization. However a GenBank entry does not meet the criteria set forth in 37 CFR 1.57 concerning appropriate sources for incorporation by reference of essential material (see MPEP 608.01(p)). The sequence of the MCOLN1 gene should be included in the sequence listing of the instant specification according to the rules governing sequence compliance (37 CFR 1.821-1.825).

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), applicant must submit a new CRF and paper copy of the Sequence Listing containing the added sequence, in addition to the previously listed sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same. Additionally, applicant shall file a 132 declaration with evidence showing and stating that the newly filed sequence is identical to the sequence that was in GenBank AF287270 at the time the invention was filed.

3. The disclosure is objected to because of the following informalities:

In Table 1 (p.10), the IVS-F primer is listed as encompassing nucleotides 5494-5509 of GenBank accession AF287270, however the primer appears to actually encompass 5495-5509.

In Table 1 (p.10), primer IVS-R is listed as encompassing nucleotides 5671-5698 of GenBank accession AF287270, however the primer appears to actually encompass 5677-5698.

On p.9, paragraph [0035], the last sentence refers to a 400 bp stretch of DNA between positions 5141 to 5941, but the positions encompass 800 bp. On p.4, paragraph [0013], lines 5-6 read 'segment of DNA that includes position 5534 between of the MCOLN1 gene'; the sentence should perhaps be edited to remove the word between.

The term TaqMan appears to be misspelled on p.15, ln.8).

Appropriate corrections are required.

Claim Objections

4. Claim 21 is objected to because of the following informalities: the claim contains the phrase 'that consists essentially of and'; the phrase may be corrected by removing the word 'and'.

Claim 22 is objected to because of the following informalities: the claim contains the phrase 'that consists essentially of and the probe in ii) is', the phrase may be corrected by removing the phrase 'and the probe in ii) is'.

Appropriate corrections are required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 19-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the claims are indefinite over the recitation of the term 'the MCOLN1 gene'. While the specification provides reference to a GenBank entry regarding the human MCOLN1 gene, neither the specification nor the sequence listing contain any information pertaining to the gene sequence, or the numbering of the nucleotides within the gene to account for descriptions of primer or probe binding sites. Reliance upon a GenBank record does not provide adequate clarity for the claimed invention, as the content and numbering in a GenBank record can change over time as the records can be updated as time passes. In this case a potential update to the cited GenBank record wherein a revision includes the addition or deletion of a single nucleotide would result in a complete change in the numbering system. In these claims, this reliance of an external GenBank sequence for a numbering scheme is similar to the recitation of a trademark, in that the GenBank accession number does not represent a fixed disclosure of a sequence, but instead refers to a record that is constantly able to be updated and modified. The application should be amended to include the appropriate MCOLN1 sequence in the sequence listing of the application. Reference to the MCOLN1 gene sequence should be via the appropriate SEQ ID NO.

7. Claims 25-34 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

Claim 25 is drawn to a method of detecting the presence of one or two mutant sequences, however steps i), ii), and iii) are so similar to steps iv), v), and vi) that it is unclear how the method would in fact detect two mutations. Additionally, the dependent claims 26 and 27 recite particular primers (SEQ ID NOs 1 and 2) which do not fall within the nucleotide positions recited in steps i) and ii) of the base claim 25. This may be corrected to more accurately represent a method for detecting two MCOLN1 mutations for which there is basis in the specification (p.4, paragraph [0013]; p.9, paragraph [0035]; p.17, paragraph [0065]) by changing steps i), ii), and iii) of claim 25 to contain the following information: step i) 'DNA between positions 5124-5524'; step ii) 'DNA between positions 5541-5941', and step iii) 'a segment of DNA that includes position 5534 of the MCOLN1 gene' (however the term 'MCOLN1 gene' should be identified by a SEQ ID NO: added to the sequence listing of the instant specification).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 19, 23-25, 28, 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edelmann et al (2002) as evidenced by GenBank AF287270 (2000) in view of Doll et al (2002).

The GenBank AF287270 sequence is the source of all nucleotide position numbers referenced in this rejection.

Edelmann et al teaches a method to screen for specific mutations (p.1023, right col., lns.14-20) responsible for causing Mucolipidosis IV. The method comprises steps of amplifying relevant portions of the MCOLN1 gene with appropriate primers (p.1024, left col., lns.26-47), and detecting the presence of wildtype or mutant gene sequences by hybridization to probes specific probes (p.1024, right col., lns.15-20).

Regarding claim 19, Edelmann et al teaches a method for determining the presence of a 6,434-bp deletion mutation spanning nucleotides 511-6,944 (designated in the reference as '511del6434') in the MCOLN1 gene. The method comprises the steps of contacting a nucleic acid sample with primers for amplification: relevant to step i) of claim 19, the MLIV-3UPS primer (p.1024, left col., lns.32-34) is complementary the 20 nucleotides from position 241 to position 260, thus satisfying the limitation of the claim that the primer is complementary to a 15-30 bp segment of DNA between positions 100-500 of the MCOLN1 gene; relevant to step ii) of claim 19, the MLIV-4UPS primer (p.1024, left col., lns.34-35) is complementary to the 20 nucleotides from position 7017 to 7036, thus satisfying the limitation of the claim that the primer is complementary to a 15-30 bp segment of DNA between positions 6956-7356 of the MCOLN1 gene. Relevant to step iii) of claim 19, Edelmann et al teaches the detection of the mutant

sequence using a probe (p.1024, right col., lns.19-20) complementary to nucleotides from positions 503-510 and positions 6944-6954, thus satisfying the limitations of the claim because the probe is complementary to a sequence that is amplified from a template DNA that possesses the 511del6434 using the primers of steps i) and ii).

Regarding claim 25, Edelmann et al teaches the multiplexing of PCR amplification for detecting the presence of one or both of the IVS3-2A→G mutation (p. 1023, right col. lns.14-16) and the 511del6434 mutation (p.1024, left col., lns.12-15; p.1024, left col., ln.47 – p.1024, right col., ln.2; Fig.1; Fig.2). The method comprises the steps of contacting a nucleic acid sample with primers for amplification, and probes for the detection of mutant sequences. **Because claim 25 has been rejected under the 112 2nd paragraph rejection earlier in this action, the examination of steps i), ii), and iii) of the claim for this art rejection assumes the correction of the claim in accordance with the specification as suggested by the examiner, and consistent with the SEQ ID NOs in the subsequent dependent claims 26-28 and 34.** Relevant to step i) of claim 25, the MLIV-1UPS primer (p.1024, left col., lns.28-29) is complementary to the 20 nucleotides from position 5361 to position 5380, thus satisfying the requirement that the primer is complementary to a 15-30 bp segment of DNA between positions 5124-5524 of the MCOLN1 gene; relevant to step ii) of claim 25, the MLIV-2UPS primer (p.1024, left col., lns.29-31) is complementary to the 20 nucleotides from position 5711 to position 5730, thus satisfying the requirement that the primer is complementary to a 15-30 bp segment of DNA between positions 5541-5941 of the MCOLN1 gene. Relevant to step iii) of claim 19, Edelmann et al teaches the

detection of the mutant sequence using a probe (p.1024, right col., ln.18) that is complementary to the 19 nucleotides from position 5523 to position 5541, thus satisfying the requirement that the probe is complementary to a segment of DNA that includes position 5534 of the MCOLN1 gene. Relevant to step iv) of claim 19, the MLIV-3UPS primer (p.1024, left col., lns.32-34) is complementary the 20 nucleotides from position 241 to position 260, thus satisfying the limitation of the claim that the primer is complementary to a 15-30 bp segment of DNA between positions 100-500 of the MCOLN1 gene; relevant to step v) of claim 19, the MLIV-4UPS primer (p.1024, left col., lns.34-35) is complementary to the 20 nucleotides from position 7017 to 7036, thus satisfying the limitation of the claim that the primer is complementary to a 15-30 bp segment of DNA between positions 6956-7356 of the MCOLN1 gene. Relevant to step vi) of claim 19, Edelmann et al teaches the detection of the mutant sequence using a probe (p.1024, right col., lns.19-20) complementary to nucleotides from positions 503-510 and positions 6944-6954, thus satisfying the limitations of the claim because the probe is complementary to a sequence that is amplified from a template DNA that possesses the 511del6434 using the primers of steps iv) and v).

Regarding claim 28, Edelmann et al teaches the sequence of the mutant IVS3-2A→G probe (p.1024, right col., ln.18), which is complementary to nucleotide positions 5523-5541of the MCOLN1 gene, thus overlaps and contains the sequence of SEQ ID NO: 6 (which is complementary to nucleotide positions 5526-5540 of the MCOLN1 gene), and thus is comprised of and consists essentially of the claimed sequence.

Regarding claim 34, Edelmann et al teaches the sequence of the 'normal' IVS3-2A→G probe (p.1024, right col., ln.17), which is complementary to nucleotide positions 5523-5541of the MCOLN1 gene, thus overlaps and contains the sequence of SEQ ID NO: 5 (which is complementary to nucleotide positions 5526-5540 of the MCOLN1 gene), and thus is comprised of and consists essentially of the claimed sequence.

Edelmann et al does not teach the detection of specific sequences (the deletion mutation, the single nucleotide mutation, or the wildtype 'normal' sequence) using probes that are labeled with detectable labels (comprising a donor fluorophore and a quencher moiety), and monitoring the accumulation of amplified nucleic acid in real time by detecting changes in fluorescence.

Doll et al teaches a method to genotype several polymorphic sites within a gene using TaqMan real time PCR analysis and probes labeled with fluorescent reporters.

Relevant to claim 19 (step iii) and part b)), claim 24, claim 25 (steps iii) and vi), and part b)), and claim 33, Doll et al teaches the detection of specific sequences using a real time PCR method in which the fluorescence signal increases when the probe with the exact sequence match binds to the template DNA and is digested by the exonuclease activity of the polymerase, thus releasing the reporter dye from the quencher (p.330, right col., ln.24 – p.331, right col., ln.6; Fig.2).

Relevant to claims 23 and 32, Doll et al specifically teaches the use of the reporter dyes FAM, VIC, and TET (p.330, left col., lns.50-56).

Relevant to claim 34, Doll et al teaches the multiplexed use of the fluorescently labeled reporter probes (p.330, right col., lns.11-24; Table 2; Fig 1) for the detection of different sequences within the same nucleic acid sample.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the mutation detection methods of Edlemann et al to have used the real time PCR detection methods of Doll et al et al. One would have been motivated to do so based on the assertion by Doll et al that the real time PCR based method is a rapid method for the analysis of nucleic acid sequences that is reliable, does not require radioactivity, and is suitable for automated applications (p.331, left col., ln.7 – p.331, right col., ln.11). One would have had a reasonable expectation of success because Doll et al teaches the successful analysis of multiple nucleic acid mutations within a given nucleic acid sample (Fig.2 of Doll et al et al) similar to the analysis of the multiple mutations of the MCOLN1 gene (Fig.2 of Edelmann et al).

10. Claims 20-22, 26, 27, and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edelmann et al (2002) in view of Doll et al (2002), and further in view of GenBank AFAF287270 (2000) and Buck et al (1999).

The teachings of Edelmann et al in view of Doll et al are applied to claims 20-22, 26, 27, and 29-31 as they were previously applied to claims 19, 23-25, 28, 32-34.

Edelmann et al teaches methods for detecting mutations in the MCOLN1 gene using primers and probes that are functionally equivalent (i.e. primers that amplify the relevant mutation-containing portions of the MCOLN1 gene, and probes that detect the

particular mutations within the MCOLN1 gene) to the primers and probes required by the claims. Specifically, Edelmann et al teaches: the MLIV-3UPS primer (p.1024, left col., lns.32-34) which has a binding site 180nt upstream of SEQ ID NO: 3 (which hybridizes to nucleotides 441-460) ; the MLIV-4UPS primer (p.1024, left col., lns.34-35), which overlaps the 20 of the 21 nucleotides in the sequence of SEQ ID NO: 4 (which hybridizes to nucleotides 7037-7017); the 511del6434 probe (p.1024, right col., lns.19-20) for detection of the sequence created by the MCOLN1 deletion mutation which has a binding site 24nt upstream of SEQ ID NO: 7 (which hybridizes to nucleotides 6982-6997); the MLIV-1UPS primer (p.1024, left col., lns.28-29) which has a binding site 50nt upstream of SEQ ID NO: 1 (which hybridizes to nucleotides 5495-5509); and the MLIV-2UPS primer (p.1024, left col., lns.29-31) which has a binding site 10nt downstream of SEQ ID NO: 2 (which hybridizes to nucleotides 5698-5677).

Edelmann et al in view of Doll et al does not teach primers comprised of sequences that consist essentially of SEQ ID NO: 3 (as required by claims 20 and 29), SEQ ID NO: 4 (as required by claims 21 and 30), SEQ ID NO: 1 (as required by claim 26), or SEQ ID NO: 2 (as required by claim 27); or a probe comprised of a sequence that consists essentially SEQ ID NO: 7 (as required by claims 22 and 31).

GenBank AF287270 teaches the complete nucleic acid sequence of the MCOLN1 gene from humans, which includes the positions of the MLIV-4UPS, MLIV-3UPS, MLIV-1UPS, and MLIV-2UPS primers and the 511del6434 probe from Edelmann et al, as well as SEQ ID NOs 1, 2, 3, 4 (paragraphs [0035]-[0036]; Table 1) and SEQ ID NO: 7 (paragraph [0050]; Table 2) from the instant application. Furthermore, Buck et al

expressly provides evidence of the equivalence of primers. Specifically, Buck et al invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al tested each of the primers selected by the methods of the different labs, Buck et al found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Therefore, it would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the detection methods of Edelmann et al in view of Doll et al to use any primers based on the MCOLN1 gene sequence of GenBank AF287270, especially sequences which are in close proximity to those taught by Edelman et al. One would have been motivated to use any appropriate primers

within the MCOLN1 sequence based on the assertion of Edelmann et al that MCOLN1 gene mutations are useful for screening for Mucolipidosis Type IV. One would have been motivated to modify the primers taught by Edelmann et al in order to have provided additional primer pairs useful in Mucolipidosis Type IV screeining. One would have had a reasonable expectation of success based on the indication of Edelmann et al that amplification and probing methods can be used to detect Mucolipidosis Type IV related mutations in the MCOLN1 gene, and the results of Buck et al that teach the successful use of primers with a wide variety of sequences.

Conclusion

No claim is free of the prior art. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached at 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Kapushoc
Art Unit 1634

JULIET C. SWITZER
PRIMARY EXAMINER